Pituitary Adenomas

9

Paolo Cappabianca, Chiara Caggiano, Domenico Solari, Karol Migliorati, Waleed A. Azab, Elia Guadagno, Marialaura Del Basso De Caro, Emmanuel Jouanneau, and Luigi M. Cavallo

Abbreviations

ACTH	Adrenocorticotropin
ASA	American Society of Anesthesiologists
AVP	Arginine vasopressin
CAD	Coronary artery disease
CSF	Cerebrospinal fluid
DI	Diabetes insipidus
FSH	Follicle-stimulating hormone
GH	Growth hormone
GTR	Gross total removal
IHD	Ischemic heart disease
LH	Luteinizing hormone
NFPA	Non-functioning pituitary adenoma
PA	Pituitary adenoma

P. Cappabianca, MD (✉) • C. Caggiano, MD • D. Solari, MD, PhD
K. Migliorati, MD • L.M. Cavallo, MD, PhD
Division of Neurosurgery, Department of Neurosciences and Reproductive and Odontostomatological Sciences, Università degli Studi di Napoli Federico II, Via Pansini 5, 80131 Naples, Italy
e-mail: paolo.cappabianca@unina.it

W.A. Azab, MD
Department of Neurosurgery, Ibn Sina Hospital, Kuwait city, Kuwait

E. Guadagno, MD • M.D.B. De Caro, BS
Department of Advanced Biomedical Sciences, Università degli Studi di Napoli Federico II, Naples, Italy

E. Jouanneau, MD, PhD
Department of Neurosurgery, University Hospital of Lyon – Hospices Civils de Lyon, Lyon, France

M. Berhouma, P. Krolak-Salmon (eds.), *Brain and Spine Surgery in the Elderly*,
DOI 10.1007/978-3-319-40232-1_9

PRL	Prolactin
SIADH	Syndrome of inappropriate antidiuretic hormone
STR	Subtotal removal
TSH	Thyroid-stimulating hormone
VDF	Visual field deficit

9.1 Introduction

Pituitary adenomas (PA) are histological benign tumours of the adenohypophysis, representing the third most frequent intracranial neoplasia [1], with equal distribution in children, adults and elderly patients. These lesions can be identified as functioning or non-functioning adenomas according to the secretion of one or more pituitary hormones by the tumour mass. Diagnosis is easily ruled out in the cases of secreting lesions, upon the clinical features of hypersecretion that define a specific phenotypic syndrome, such as Cushing disease or acromegaly; conversely, in cases of non-functioning tumours, lesions are diagnosed when symptoms due to the mass effect, i.e. visual defects and/or oculomotor palsy, become evident. Finally, it should not be underestimated that a certain percentage of patients remain totally asymptomatic, receiving though accidental diagnosis.

The frequency of different subtypes of PA differs among age groups: the most common PAs in early childhood are ACTH-secreting; prolactinomas are the most encountered during the second, third and fourth decades of life, while after the age of 40 years, the most frequent are the non-functioning pituitary adenomas (NFPAs).

Nowadays, the average life can exceed 75 years in the developed countries and may increase in the future decades, with the threshold of elderly being considered 65 years. The incidence of PAs in this group of patients, i.e. the elderly, ranges between 7 and 9.9 % [12]: it is actually increasing, mostly due to the expanding number of elderly among population and to the increasing use of "secondary line" diagnostic tools, namely, the MRI for other neurological diseases, such as senile dementia, Alzheimer disease, cerebral transient ischemic attack, stroke, etc. [20]. As a matter of fact, non-functioning tumours represent the 70–80 % of all PAs in the elderly [2, 12, 17, 24, 26] and the main presenting symptoms are visual defects [12, 22, 31]. Otherwise, the most common functioning lesions in these patients are GH-secreting (14 %) and ACTH-secreting (4 %) [12].

9.2 Clinical Features

PAs in elderly are mainly represented by NFPAs, so that the most common symptoms observed at diagnosis are related to the mass effect: headache (29–43 %), visual field defects (VFD) and/or visual acuity loss (40–87 %) due to the compression of the optic chiasm and pathways and/or hypopituitarism (50–60 %) [20]. These clinical signs are often misdiagnosed, considering the presence of the different co-morbidities the elderly patients complain of.

In Table 9.1 the clinical features of elderly patients with PA as reported in literature are summarized. Other clinical presentations include pituitary intralesional

Table 9.1 The summary of the clinical feature series of elderly patients with PA in the last 20 years

Study	Visual symptoms	Endocrinological status	Others	Incidentally detected tumours	Time for diagnosis
Puchner (1995)	–	↑GH 100 %	NR	NR	NR
Benbow (1997) [2]	54.50 %	↑GH 11.3 % ↓TSH 33.3 % ↓ACTH 48.7 % ↑PRL 4.5 %	Neurological 20.45 % Apoplexy 2.2 %	15.90 %	NR
Turner (1999) [31]	39.3 %	Hypopituitarism 20.20 %	Hypernatraemia 9.5 %	9.50 %	NR
Fraioli (1999)	81.80 %	Hypopituitarism 90 %	III c.n. paralysis 9 %	NR	NR
Minniti (2005) [22]	66.6 %	↑PRL 100 %	Headache 33.3 % Cerebral ischaemia 11.1 %	NR	NR
Hong (2008) [14]	86.4 %	Hypopituitarism (35.9 %)	Headache 47.6 %	–	5.7years ±1.3 years
Sheehan (2008) [26]	58 %	↑GH 5 %	–	9 %	NR
Locatelli (2013) [21]	44 %	Hypopituitarism 44.1 % Single defect 30.2 % Multiple defect 13.9 %	–	–	–
Zhan (2015) [32]	84.2 %	–	Headache 75.9 %	NR	NR
Pereira (2014)	41.3 %	↑GH 3.8 % ↑ACTH 1.4 % ↓TSH 7.6 % ↓LH-FSH 1 % Hypopituitarism 3.8 %	Headache 5.8 % Apoplexy 3.8 %	22.5 %	NR
Gondim (2015) [12]	69 %	Hypopituitarism 38.2 %	Headache 29 % Apoplexy 10.9 %	–	–
Liu (2015) [20]	–	↑1 or more pituitary hormone 6.3 % ↓1 or more pituitary hormone 3.1 %	Mass effect 98.4 %	10.1 %	<5 years 64.5 % 5–10 years 21 % >10 years 14.5 %

haemorrhage/apoplexy (11–30 %) and/or ophthalmoplegia (3–10 %). Pituitary apoplexy occurs often in large adenomas and it results common in elderly as related to their co-morbidities, such as hypertension and coronary heart diseases, which are predisposing factors [20].

Visual deficit is the primary symptom in the majority of the published trials: different patterns of VFD have been described in patients with PA, in regard to the relationships between the tumour and the optic pathway. The most common VFD, also in the elderly patients with PA, is bitemporal hemianopia: the defect may be complete, involving the whole temporal field, or partial, usually affecting the superior quadrant. Anterior lesions, impinging pre-chiasmatic nerve, can cause central scotomas, while posterior lesions involving the optic tract can provide homonymous hemianopia. Despite several studies confirm that bitemporal hemianopia is the most prevalent VFD in elderly patients complaining of non-functioning tumours, it is quite common that this defect goes misdiagnosed [23]. Retinal degeneration, cataracts and amblyopia are common visual disturbances in the elderly: therefore, visual disturbances related to compression of optic pathways caused by the NFPA may be initially attributed to other age-related visual conditions and/or be unrecognized [6, 14].

Although clinical manifestations of hypopituitarism are not clearly evident, blood tests reveal in most cases pituitary function partial or complete hormonal failures. The majority of the studies show that most of the affected pituitary axes are the gonadic, with low LH/FSH levels in about 60 % of the cases, as well as the somatotrophic, with low IGF-1 levels in 50 % of the cases [7, 17]. On the other hand, the adrenocorticotrophic and thyrotrophic axes were deficient in about, respectively, 27 % and 23 % of the cases [7, 14, 31].

9.3 Preoperative Considerations

Preoperative evaluation must consider three main aspects:

- The type and size of PA
- The eventual patient co-morbidities
- The ASA (American Society of Anesthesiologists) score

As already mentioned, PAs in elderly are mostly NFPAs [14, 19, 20, 24, 31] generally large, but do not present more aggressive features as compared to those occurring in the younger patients [15, 20]: decrease of cell proliferation rate has been observed in adenomas, especially NFPA and GH-secreting tumours [15] of the elderly.

The main characteristics, i.e. tumour size, localization and type of adenomas, are summarized in Table 9.2.

The incidence of associated co-morbidities is highly variable (ranging from 17 to 90 %) with cardiovascular diseases being the most frequent, followed by respiratory diseases, diabetes mellitus and neurological disorders [21]. Most of these patients receive long-standing treatment with cardiological drugs, such as antihypertensive or

Table 9.2 Main tumour characteristics of PA in elderly patients

Study	Location	Size	Type
Fraioli (1999)	Intrasellar 9 % Intra-suprasellar 81,8 %	<1 cm 9 % >1 cm 91 %	NF 72,7 % PRL 9 % GH 9 % ACTH 9 %
Hong (2008) [14]	–	1–2 cm 6.8 % 2–3 cm 49.5 % 3–4 cm 35.9 % >4 cm 7.8 %	NF 72.8 % GH 9.7 % PRL 15.5 % ACTH 1.9 %
Locatelli (2010)	–	>1 cm 90.6 % >1 cm 9.4 %	NF 72 % GH 9.4 % ACTH18.6
Zhan (2015) [32]	Intrasellar 15.8 % Intra-suprasellar 40.5 % Parasellar 18.4 % Supra-parasellar 25.3 %	>1 cm 84.2 % <1 cm 15.8 %	NF 100 %
Gondim (2015) [12]	Knosp 2 5.4 % Knosp 3 9 % Knosp 4 14.5 %	–	NF 78.5 % GH 14.2 % PRL 2.8 % ACTH 4.2 %
Liu (2015) [20]	–	>1 cm 85.5 % >4 cm 14.5 %	NF 75.4 % GH 5.8 % ACTH 10.1 % Plurihormonal 5.8 % Apoplexy 2.9 %

antiarrhythmic agents, and a conspicuous number of patients in this group (59.4 %) complain of more than two co-morbidities: these factors can determine a longer preoperative hospitalization. Besides, endocrine and metabolic disorders, including significant changes in the hypothalamo-pituitary axis and pancreatic and thyroid malfunctioning, should be taken into account [18]; approximately 40 % of individuals between 65 and 74 years and ca. 50 % of individuals older than 80 years present impaired glucose tolerance or diabetes mellitus, often undiagnosed [16] (Table 9.3).

For these reasons, the preoperative clinical status of elderly patients with PA is commonly defined with ASA score of three or even four (Table 9.4), although there is no significant difference in terms of mortality (p 0.12) between young and elderly patients.

Owing that, surgery for the removal of a pituitary adenoma in an elderly can be indicated when patients present clear symptoms related to the adenoma, without severe co-morbidities that increase too much the overall risks of surgery.

It is preferable to choose a surgical approach as minimal invasive as possible, according to the localization and the inner features of the lesion. Nowadays, the endoscopic endonasal transsphenoidal approach represents a good option for the surgical treatment of pituitary adenomas in the elderly, because of its effectiveness in terms of tumoral removal, the excellent surgical outcomes in terms of visual outcome, its minimal invasiveness and the lower rates of morbidity and mortality related to the approach.

Table 9.3 Main co-morbidity in elderly patients with PA

Study	Co-morbidity
Hong (2008) [14]	Hypertension 33.9 %
	Cardiac disease 1.9 %
	Respiratory disease 23.3 %
	Hyperglycaemia 41.7 %
Sheehan (2008) [26]	Hypertension 26.9 %
	Cardiac disease 21.4 %
	Respiratory disease 8.3 %
	Coexisting malignancy 8.3 %
Locatelli (2013) [21]	Cardiac disease 86 %
	Respiratory disease 60.5 %
	Diabetes mellitus 18.6 %
	Neurological disease 11.6 %
Pereira (2014)	Hypertension 61.2 %
	Cardiac disease 10.7 %
	Hypercholesterolaemia 15.7 %
	Coexisting malignancy 13.7 %
	Diabetes mellitus 13 %
	Arthrosis 10.7 %

Table 9.4 Main complications after endoscopic endonasal transsphenoidal surgery

Authors	General complications	Specific complications
Turner (1999) [31]	Myocardial infarction 1.2 % Chest infection 1.2 % Small gastrointestinal bleed 1.2 % Meningitis 1.2 %	Transient DI 2.38 % Permanent DI 4.76 % Deterioration of visual function 5.9 %
Hong (2008) [14]	None	Transient DI 37.9 % CSF leak 4.9 % Deterioration of visual function 9.7 % Postoperative hypopituitarism 10.7 %
Sheehan (2008) [26]	None	DI 3.12 % Hypocortisolism 1.5 % Hypothyroidism 4.7 %
Grossman (2010) [13]	Death 3.75 % Pulmonary complications 3.50 % Stroke 2.52 %	Fluid or electrolyte abnormality 14.32 % CSF rhinorrhea 5.38 % DI 1.15 % Panhypopituitarism 0.5 %
Zhan (2015) [32]	None	DI 22.2 % CSF leak 3.8 % New hypopituitarism 9.5 % Meningitis 1.9 %
Liu (2015) [20]	Severe systemic complications (Clavien Classification ≥ IV) 4.3 %	DI 11.6 % CSF leak 1.4 % Panhypopituitarism 4.3 %
Gondim (2015) [12]	Refractory hypertension (7.2 %) Myocardial ischaemia (1.8 %)	CSF leaks (9 %), DI (3.6 %) Hypopituitarism 12.7 %

9.4 Surgical Technique and Outcome

Surgery yields the best outcomes when performed in dedicated centres, and it's targeted to achieve multiple goals, such as elimination of mass effect, restoration of normal pituitary function and/or visual acuity, prevention of tumour recurrence and normalization of excess of hormone secretion.

After general anaesthesia and orotracheal intubation, the patient is positioned supine with the head at 0° and rotated 10° to the surgeon. Disinfection with povidone-iodine into the nasal cavities and on the nasal skin is performed. Then eight cottonoids drenched of a solution with 2 ml of adrenaline 0.5 % and 5 ml of lidocaine are introduced into the nasal cavities and the draping is performed. In patients with history of ischemic heart disease (IHD) or coronary artery disease (CAD), we prefer to not use adrenaline in such solution for nasal decongestion. The technique consists in three parts: nasal, sphenoidal and sellar step [3, 4, 8, 28, 29].

- Nasal step
  We generally use a 0° angled lens, 4 mm in diameter endoscope, that is inserted in the right and then in the left nostril, between the nasal septum medially and the middle turbinate laterally. The cottons are then removed to promote the anti-bleeding effect, avoiding the nasal mucosa ischaemia, and the middle turbinate is carefully lateralized to increase the surgical corridor. Usually, in elderly patients the nasal mucosa and its vascular network appear hypotrophic, so that the nasal cavities are easily explored with the endoscope. Once the nasal choana is reached, the endoscope is pushed up for about 1.5–2 cm to identify the sphenoethmoid recess and the ostium of the sphenoid sinus.
- Sphenoidal step
  Once the mucosa is coagulated, the sphenoethmoid recess is opened and the posterior part of nasal septum is removed to expose the cavity of sphenoid sinus. The sphenoid mucosa is extensively removed to avoid postoperative sphenoid mucocele. After removal of eventual septa inside the sinus, several important anatomical landmarks are visible: at the centre the protuberance of the sellar floor, laterally the carotid protuberances, above the planum and below the clivus; above the carotid protuberance, there is the optic protuberance and between them the opto-carotid recess that corresponds to the anterior clinoid.
- Sellar step
  We generally perform this phase with four hands-two surgeons technique. The sellar opening is performed by microdrilling and can be extended up to the clivus below or the planum above, depending on the extension of the adenoma. The dural incision is performed in a cruciate fashioned at the midline. The adenoma is frequently soft and can be removed by suction and curetting, starting from the inferior and lateral parts, to retard the descent of the suprasellar cistern. After tumour removal, the osteodural defect is repaired depending to the opening entity and the presence of intraoperative CSF leak. In case of large macroadenomas, the bone exposure can involve the planum sphenoidale. In these cases the subarachnoid space is intentionally violated, and, because the surgery is performed through the basal cisterns, intraoperative CSF leakage occurs. However,

the goal of the reconstruction is a watertight closure of the skull base defect, to avoid postoperative CSF leak and infective complications.
It should be minded that in elderly patients, it is preferable to avoid opening of the suprasellar cistern, while accepting the risk of an incomplete tumour removal. This choice mostly relies on the fact that on one side the osteodural defect could be troublesome and take longer, but on the other the tumour growth is extremely slow.

9.5 Postoperative Management

All the patients, regardless the age, are generally mobilized on the same day of surgery.

The visual field deficits usually improve and/or are fully recovered, even if the defects were lasting for more than 6 months [20, 21]. Conversely, endocrine functions, above all in patients with preoperative hypopituitarism, do not change, maybe for a limited pituitary functional reserve in the elderly population [12, 20, 24].

The mean postoperative hospitalization stay is not different between elderly and young patients [12, 21].

Zhan et al. reported a total resection in 75.9 % of patients, subtotal resection in 22.8 % and a partial resection in 1.3 %, after pure endoscopic transsphenoidal surgery, with no significant difference compared to the younger group of control [32]. Also Gondim et al. in their series of elderly patients didn't find significant difference between the extent of resection obtained in elderly and young patients [12].

Postoperative fractionated radiotherapy is frequently administered to patients with residual or recurrent pituitary disease, but it is not recommended after surgery in elderly patients, considering the slow tumour growth rate, the low incidence of recurrences following total or subtotal resection and the shorter expectancy of life in this category of patients [30].

The use of adjuvant radiotherapy may be considered only in patients with large residual tumour that are unresponsive to medical treatment, although no consensus guidelines are available [22]. Chang et al. indeed recommend the use of adjuvant radiotherapy only in case of subtotal removal (STR), especially if the cavernous sinus is invaded, while not in case of gross total removal (GTR), due to the increased risk of death [5].

9.6 Complications

9.6.1 Medical Complications

Cardiopulmonary and vascular diseases, thromboembolic events, postoperative pneumonia, sepsis, stress ulcer bleeding, stroke and death represent the main dreaded postsurgical complications, when an elderly patient is submitted to a surgical procedure for the removal of a pituitary adenoma.

As previously reported, elderly patients have a higher rate of co-morbidities and are prone to develop systemic complications, so that incidence rates of complications are not claimed univocal.

Locatelli et al. reported the absence of major surgical complications, although about 70 % of patients had moderate or severe risk according to ASA class – this series accounts on 11 % of patients belonging to ASA score categories 4 and 5 [21].

Contrariwise, Gondim et al. reported a rate of systemic complications of 32.7 % in elderly group versus 10 % in younger patients, being this difference statistically significant ($p < 0.05$). In this study, the higher rate of complications in elderly was referred to the postoperative high blood pressure peaks and subclinical pituitary apoplexy that occurs more frequently in elderly people; however, no significant mortality rate difference was observed between the two groups [12].

9.6.2 Approach-Related Complications

Potential complications of the endoscopic endonasal surgery include diabetes insipidus (DI) (11.6 %), postoperative hypopituitarism (22 %), cerebrospinal fluid (CSF) leak (5–16 %), meningitis (5.5 %), visual impairment (1.5 %), syndrome of inappropriate antidiuretic hormone (SIADH) secretion (8.5–25 %), haemorrhage (5 %), carotid artery injury (<1 %), ischemic stroke (2 %) and epistaxis (4.8 %) [12, 20] (Table 9.4).

Concerning endocrinological complications, postoperative DI results the most common: it can be transient, permanent or triphasic. Transient DI (30 % of patients) has its onset at 24–48 h post-op and it is usually resolved in 3–5 days. Permanent DI (10 % of cases) can be seen in patients in whom there is a direct damage to the pituitary stalk, hypothalamus and/or proximal infundibulum. The triphasic DI is extremely rare, with a first phase like transient DI and a second similar to SIADH, and finally it develops permanent DI. Untreated DI can cause or worsen hypernatraemia and serum hyperosmolality, potentially leading to dehydration, lethargy, irritability and, in the case of severe hypernatraemia, seizures [9, 25]. On the other side, as reported by Liu et al., there is no significant difference of postsurgical hypopituitarism rates between old and young patients [20].

Finally, notwithstanding recent advancements of the techniques and materials, CSF leak remains a frequent complication of this kind of surgery, also in elderly patients [11–13, 17]. It should be said though that intraoperative CSF fistula is the only significant predictive factor of postoperative leakage [10]: this complication is usually rare during removal manoeuvres of infradiaphragmatic lesions, whereas its risk raises when dealing with lesions that have breached the diaphragm. In these latter cases, an accurate reconstruction is mandatory of the osteodural defect [27].

Conclusion

Surgery in the elderly group is recommended for pituitary tumours causing neurological deficits – above all visual – and endocrinological syndrome, eventually resistant to pharmacological treatment. The endoscopic endonasal approach is

the gold standard because of its safeness and efficacy. No mortality or major complications are observed, even in patients with elevated ASA scoring class; multiple co-morbidities, however, should be taken into account preoperatively, to achieve a long-term successful outcome and avoid threatening morbidities related to the surgery and to the approach itself. An adequate preoperative planning, careful surgical technique and rigorous postoperative care can reduce mortality and morbidity rates in this high-risk patient group.

References

1. Asa SL, Ezzat S (2002) The pathogenesis of pituitary tumours. Nat Rev Cancer 2(11):836–849. doi:10.1038/nrc926
2. Benbow SJ, Foy P, Jones B, Shaw D, MacFarlane IA (1997) Pituitary tumours presenting in the elderly: management and outcome. Clin Endocrinol (Oxf) 46(6):657–660
3. Cappabianca P, Cavallo LM, Colao A, Del Basso De Caro M, Esposito F, Cirillo S, Lombardi G, de Divitiis E (2002) Endoscopic endonasal transsphenoidal approach: outcome analysis of 100 consecutive procedures. Minim Invasive Neurosurg MIN 45(4):193–200. doi:10.1055/s-2002-36197
4. Cappabianca P, Cavallo LM, Solari D, Stagno V, Esposito F, de Angelis M (2014) Endoscopic endonasal surgery for pituitary adenomas. World Neurosurg 82(6 Suppl):S3–S11. doi:10.1016/j.wneu.2014.07.019
5. Chang EF, Zada G, Kim S, Lamborn KR, Quinones-Hinojosa A, Tyrrell JB, Wilson CB, Kunwar S (2008) Long-term recurrence and mortality after surgery and adjuvant radiotherapy for nonfunctional pituitary adenomas. J Neurosurg 108(4):736–745. doi:10.3171/JNS/2008/108/4/0736
6. Christensen K, Doblhammer G, Rau R, Vaupel JW (2009) Ageing populations: the challenges ahead. Lancet 374(9696):1196–1208. doi:10.1016/S0140-6736(09)61460-4
7. Del Monte P, Foppiani L, Ruelle A, Andrioli G, Bandelloni R, Quilici P, Prete C, Palummeri E, Marugo A, Bernasconi D (2007) Clinically non-functioning pituitary macroadenomas in the elderly. Aging Clin Exp Res 19(1):34–40
8. Di Maio S, Cavallo LM, Esposito F, Stagno V, Corriero OV, Cappabianca P (2011) Extended endoscopic endonasal approach for selected pituitary adenomas: early experience. J Neurosurg 114(2):345–353. doi:10.3171/2010.9.JNS10262
9. Dumont AS, Nemergut EC 2nd, Jane JA Jr, Laws ER Jr (2005) Postoperative care following pituitary surgery. J Intensive Care Med 20(3):127–140. doi:10.1177/0885066605275247
10. Duntze J, Litre CF, Graillon T, Maduri R, Pech-gourg G, Rakotozanany P, Gras R, Dufour H (2012) Cerebrospinal fluid rhinorrhea following endocopic trans-sphenoidal pituitary surgery: experience from 337 patients. Neurochirurgie 58(4):241–245. doi:10.1016/j.neuchi.2012.02.005
11. Ferrante L, Trillo G, Ramundo E, Celli P, Jaffrain-Rea ML, Salvati M, Esposito V, Roperto R, Osti MF, Minniti G (2002) Surgical treatment of pituitary tumors in the elderly: clinical outcome and long-term follow-up. J Neurooncol 60(2):185–191
12. Gondim JA, Almeida JP, de Albuquerque LA, Gomes E, Schops M, Mota JI (2015) Endoscopic endonasal transsphenoidal surgery in elderly patients with pituitary adenomas. J Neurosurg 123(1):31–38. doi:10.3171/2014.10.JNS14372
13. Grossman R, Mukherjee D, Chaichana KL, Salvatori R, Wand G, Brem H, Chang DC, Quinones-Hinojosa A (2010) Complications and death among elderly patients undergoing pituitary tumour surgery. Clin Endocrinol (Oxf) 73(3):361–368. doi:10.1111/j.1365-2265.2010.03813.x
14. Hong J, Ding X, Lu Y (2008) Clinical analysis of 103 elderly patients with pituitary adenomas: transsphenoidal surgery and follow-up. J Clin Neurosci Off J Neurosurg Soc Australasia 15(10):1091–1095. doi:10.1016/j.jocn.2007.11.003
15. Jaffrain-Rea ML, Di Stefano D, Minniti G, Esposito V, Bultrini A, Ferretti E, Santoro A, Faticanti Scucchi L, Gulino A, Cantore G (2002) A critical reappraisal of MIB-1 labelling index significance in a large series of pituitary tumours: secreting versus non-secreting adenomas. Endocr Relat Cancer 9(2):103–113

16. Kuchel GA, Minaker KL (1990) Dizziness in geriatric practice. J Am Geriatr Soc 38(8):957
17. Kurosaki M, Saeger W, Ludecke DK (2001) Pituitary tumors in the elderly. Pathol Res Pract 197(7):493–497. doi:10.1078/0344-0338-00117
18. Lamberts SW, van den Beld AW, van der Lely AJ (1997) The endocrinology of aging. Science 278(5337):419–424
19. Letournel F, Menei P, Guy G, Saint-Andre JP (2003) Transsphenoidal surgery in the elderly. J Am Geriatr Soc 51(5):729–730
20. Liu J, Li C, Xiao Q, Gan C, Chen X, Sun W, Li X, Xu Y, Chen J, Shu K, Lei T (2015) Comparison of pituitary adenomas in elderly and younger adults: clinical characteristics, surgical outcomes, and prognosis. J Am Geriatr Soc 63(9):1924–1930. doi:10.1111/jgs.13590
21. Locatelli M, Bertani G, Carrabba G, Rampini P, Zavanone M, Caroli M, Sala E, Ferrante E, Gaini SM, Spada A, Mantovani G, Lania A (2013) The trans-sphenoidal resection of pituitary adenomas in elderly patients and surgical risk. Pituitary 16(2):146–151. doi:10.1007/s11102-012-0390-z
22. Minniti G, Esposito V, Piccirilli M, Fratticci A, Santoro A, Jaffrain-Rea ML (2005) Diagnosis and management of pituitary tumours in the elderly: a review based on personal experience and evidence of literature. Eur J Endocrinol/Eur Fed Endocrine Soc 153(6):723–735. doi:10.1530/eje.1.02030
23. Ogra S, Nichols AD, Stylli S, Kaye AH, Savino PJ, Danesh-Meyer HV (2014) Visual acuity and pattern of visual field loss at presentation in pituitary adenoma. J Clin Neurosci Off J Neurosurg Soc Australasia 21(5):735–740. doi:10.1016/j.jocn.2014.01.005
24. Robenshtok E, Benbassat CA, Hirsch D, Tzvetov G, Cohen ZR, Iraqi HM, Gorshtein A, Toledano Y, Shimon I (2014) Clinical course and outcome of nonfunctioning pituitary adenomas in the elderly compared with younger age groups. Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinologists 20(2):159–164. doi:10.4158/EP13182.OR
25. Schreckinger M, Szerlip N, Mittal S (2013) Diabetes insipidus following resection of pituitary tumors. Clin Neurol Neurosurg 115(2):121–126. doi:10.1016/j.clineuro.2012.08.009
26. Sheehan JM, Douds GL, Hill K, Farace E (2008) Transsphenoidal surgery for pituitary adenoma in elderly patients. Acta Neurochir 150(6):571–574. doi:10.1007/s00701-008-1581-2; discussion 574
27. Shiley SG, Limonadi F, Delashaw JB, Barnwell SL, Andersen PE, Hwang PH, Wax MK (2003) Incidence, etiology, and management of cerebrospinal fluid leaks following trans-sphenoidal surgery. Laryngoscope 113(8):1283–1288. doi:10.1097/00005537-200308000-00003
28. Solari D, Cavallo LM, Cappabianca P (2014) Surgical approach to pituitary tumors. Handb Clin Neurol 124:291–301. doi:10.1016/B978-0-444-59602-4.00019-8
29. Solari D, Cavallo LM, De Angelis M, Villa A, Somma T, Esposito F, Del Basso De Caro M, Cappabianca P (2012) Advances in trans-sphenoidal pituitary surgery. Panminerva Med 54(4):271–276
30. Tanaka Y, Hongo K, Tada T, Sakai K, Kakizawa Y, Kobayashi S (2003) Growth pattern and rate in residual nonfunctioning pituitary adenomas: correlations among tumor volume doubling time, patient age, and MIB-1 index. J Neurosurg 98(2):359–365. doi:10.3171/jns.2003.98.2.0359
31. Turner HE, Adams CB, Wass JA (1999) Pituitary tumours in the elderly: a 20 year experience. Eur J Endocrinol/Eur Fed Endocrine Soc 140(5):383–389
32. Zhan R, Ma Z, Wang D, Li X (2015) Pure endoscopic endonasal transsphenoidal approach for nonfunctioning pituitary adenomas in the elderly: surgical outcomes and complications in 158 patients. World Neurosurg 84(6):1572–1578. doi:10.1016/j.wneu.2015.08.035